DOI 10.31489/2023BMG3/35-48

UDC 577.29

O.V. Bulgakova*, N.B. Rezhepova

L.N. Gumilyov Eurasian National University, Astana, Kazakhstan
**Corresponding author: ya.summer13@yandex.kz*

Molecular mechanisms of radiation-induced aging

Radiation-induced aging is a complex process that involves multiple molecular mechanisms. One of the primary mechanisms underlying radiation-induced aging is oxidative stress. Exposure to radiation can lead to the generation of reactive oxygen species (ROS), which can cause damage to DNA, proteins, and other cellular components. In addition to these mechanisms, radiation-induced aging can also involve alterations in gene expression, cellular metabolism, and epigenetic modifications. These changes can affect the function of various cellular pathways and contribute to the aging process. Understanding the molecular mechanisms of radiation-induced aging is critical for developing strategies to mitigate its effects. Potential interventions include targeting oxidative stress, promoting DNA repair, altering the epigenetic landscape and modulating cellular metabolism. However, further research is needed to fully elucidate the complex molecular pathways involved in radiation-induced aging and identify effective therapeutic approaches. In general, the molecular mechanisms of radiation's impact on aging discussed in this review provide a new perspective on radiation-induced aging and identify new targets for intervention.

Keywords: aging, DNA damage, telomeres, Mitochondrion, MicroRNA, Inflammation, p16, Radiation-induced aging.

Introduction

Aging is a complex, multifaceted process leading to widespread functional decline affecting every organ and tissue. Remarkably, it is still unknown whether aging has a unifying causal mechanism or whether it is based on multiple sources. Phenotypically, the aging process is associated with a wide range of features at the molecular, cellular, and physiological level, such as genomic and epigenomic changes, loss of proteostasis, decreased overall cellular and subcellular function, and impaired regulation of signaling systems. DNA damage is the driving force behind aging. The nuclear and mitochondrial genomes are constantly damaged by external agents (UV, X-rays, chemical compounds in food, water, air), endogenous sources such as reactive oxygen species (ROS), aldehydes and glycation end products (AGEs) and spontaneous reactions (hydrolysis). Molecular consequences of the time-dependent accumulation of DNA damage are (i) genetic aberrations such as mutations and chromosomal instability, and (ii) shutdown of RNA and DNA polymerases by DNA damage, which provokes DNA damage signaling and disrupts primary DNA function. Cellular and tissue consequences of DNA damage include cell fate decisions such as cell death and aging, leading to functional cell and organ loss, cancer, atrophy and inflammation [1].

Old age became a major risk factor for very common chronic and devastating diseases, including cancer, cardiovascular and neurodegenerative diseases. Classically, the aging process is characterized by several possible features, including genomic damage and telomere shortening, epigenetic changes, dysregulation of proteostasis, mitochondrial dysfunction, stem cell pool collapse, intercellular communication disorder and cellular aging [2].

Cell aging appears as an irreversible loss of replicative potential of primary cells in culture, initiated as a persistent DNA damage response to dysfunctional telomeres [3].

The environment, especially early life events, is important modifiers of the aging process. Since the genetic mechanisms underlying aging are not controllable, understanding how environmental factors slow or accelerate the aging process is of great practical importance.

Radiation-induced aging refers to the premature aging and degeneration of tissues and organs caused by exposure to ionizing radiation. The cellular and molecular mechanisms underlying radiation-induced aging are complex and not fully understood. However, some of the key mechanisms that were proposed included:

DNA damage: Ionizing radiation can cause direct damage to DNA, leading to mutations and chromosomal abnormalities. These mutations can accumulate over time and contribute to aging and age-related diseases.

Oxidative stress: Radiation exposure can increase the production of reactive oxygen species (ROS) in cells, leading to oxidative stress and damage to cellular components such as proteins, lipids, and DNA.

Inflammation: Radiation exposure can trigger an inflammatory response in tissues, leading to chronic inflammation and tissue damage over time.

Epigenetic changes: Radiation exposure can cause changes in gene expression patterns by altering the epigenetic marks on DNA, such as DNA methylation and histone modifications.

DNA damage

These mechanisms can interact and amplify each other, leading to the cumulative effects of radiation-induced aging. While the exact mechanisms may vary depending on the dose and type of radiation, understanding the cellular and molecular mechanisms of radiation-induced aging is important for developing effective strategies to mitigate its negative effects. Ionizing radiation can cause various types of DNA damage, including single-strand breaks, double-strand breaks, base damage, and crosslinking. These types of damage can lead to mutations, chromosomal abnormalities, and other changes in DNA structure and function.

Of these types of damage, double-strand breaks (DSBs) are considered the most dangerous and difficult to repair. DSBs can lead to cell death, chromosomal rearrangements, and mutations, all of which contribute to aging and age-related diseases.

TP53 is a tumor suppressor gene that plays a key role in the DNA damage response. When DSBs occur, TP53 is activated and triggers cell cycle arrest or apoptosis to prevent the propagation of damaged cells. However, TP53 expression declines with age, which can lead to increased genomic instability and age-related diseases [4].

ATM and ATR are protein kinases that are also involved in the DNA damage response. They are activated by DSBs and help to repair the damage by coordinating DNA repair pathways. Defects in ATM and ATR were linked to premature aging syndromes, such as ataxia-telangiectasia and Seckel syndrome [5].

WRN is a helicase enzyme that is involved in DNA repair and maintenance. It plays a role in repairing DSBs through non-homologous end joining (NHEJ) and homologous recombination (HR) pathways. Mutations in WRN are associated with Werner syndrome, a rare genetic disorder characterized by premature aging and age-related diseases [6].

Ku70 and Ku80 are subunits of a protein complex called Ku, which is involved in NHEJ repair of DSBs. Defects in Ku70 and Ku80 were linked to premature aging and age-related diseases, such as progeria and dyskeratosis congenita [7].

These are just a few examples of how DSBs can impact gene expression and contribute to aging [8]. However, it's worth noting that the relationship between DNA damage and aging is complex and multifaceted, and there are likely many other genes and pathways involved.

Several types of ionizing radiation can cause DSBs in DNA, including:

X-rays are a type of electromagnetic radiation that can penetrate tissues and cause ionization of atoms and molecules, leading to DSBs in DNA.

Gamma rays are high-energy photons emitted by radioactive isotopes. They can also penetrate tissues and cause ionization and DNA damage.

Alpha particles are high-energy helium nuclei that are emitted by some radioactive isotopes. They have a relatively short range and can cause DSBs when they collide with DNA.

Beta particles are high-energy electrons or positrons emitted by some radioactive isotopes. They can penetrate tissues to varying degrees and cause ionization and DNA damage.

The amount of DSBs caused by ionizing radiation depends on various factors, such as the energy and dose of the radiation, the type of tissue being exposed, and the duration of exposure. The ability of cells to repair DSBs also varies depending on the type of radiation and the cell type. Nonetheless, DSBs are considered one of the most serious types of DNA damage caused by ionizing radiation, and they can have long-term effects on cell function and contribute to aging and age-related diseases [9].

Radiation can also cause oxidative damage to DNA, leading to the formation of 8-hydroxyguanine (8-OHdG), a type of base damage that can cause mutations and lead to aging. 8-OHdG is a type of oxidative DNA damage that occurs when ROS react with guanine in DNA. ROS are generated by various cellular processes, such as metabolism and inflammation, as well as by exposure to ionizing radiation and environmental toxins. 8-OHdG can cause mutations and other types of DNA damage, which can contribute to aging and age-related diseases [10].

There is evidence that levels of 8-OHdG increase with age in various tissues, including the brain, liver, and kidney. This suggests that oxidative damage to DNA may play a role in the aging process. In addition, several studies linked higher levels of 8-OHdG to age-related diseases such as cardiovascular disease, neurodegenerative diseases, and cancer.

One mechanism by which 8-OHdG may contribute to aging is by interfering with DNA repair mechanisms [11] 8-OHdG can disrupt the structure of DNA and interfere with the activity of enzymes involved in DNA repair, making it more difficult for cells to fix other types of damage. This can lead to further accumulation of DNA damage and contribute to the aging process.

Overall, while the exact role of 8-OHdG in aging is still being studied, there is evidence to suggest that this type of oxidative DNA damage may contribute to age-related changes in cellular function and the development of age-related diseases.

In addition to these specific types of DNA damage, radiation exposure can also lead to more general changes in DNA structure and function, such as altered epigenetic marks and changes in gene expression patterns, which can also contribute to aging.

Epigenetic changes

There is evidence to suggest that exposure to ionizing radiation can alter global DNA methylation levels, but the exact nature of these changes can depend on various factors, including the dose and duration of radiation exposure, the type of cells exposed, and the timing of exposure.

Both aging and ionizing radiation exposure were shown to affect DNA methylation patterns in various ways.

With regards to aging, research showed that there was a general decrease in DNA methylation levels with age, which could lead to changes in gene expression and contribute to age-related diseases such as cancer. Specific genes and regions of the genome were identified as being particularly affected by age-related DNA methylation changes.

Regarding ionizing radiation exposure, research showed that exposure to radiation could induce changes in DNA methylation patterns. Studies reported both increases and decreases in DNA methylation levels following radiation exposure, depending on the dose, timing, and specific tissue or cell type studied. Those changes in DNA methylation were linked to altered gene expression and potentially increased cancer risk [12].

Some studies reported that exposure to ionizing radiation could lead to global hypomethylation, which was a reduction in the overall level of DNA methylation. For example, one study showed that low-dose radiation exposure in mice led to a decrease in global DNA methylation levels in multiple tissues [13]. Another study found that radiation exposure led to a decrease in DNA methylation levels in blood samples from workers who had been exposed to radiation [14].

Radioactive contamination is a significant factor affecting the environment and human health. For the Republic of Kazakhstan, the issues of radiation safety of the population are very relevant, since the Semipalatinsk nuclear test site has been operating on the territory of our country for a long time. During the testing period, several hundred thousand people were repeatedly exposed to it [15], and these consequences of nuclear explosions pose a serious threat to the health of the population of Kazakhstan. In addition to technogenic contamination, Kazakhstan also has a very high level of natural radiation exposure of the population. For example, in the north of the country there is the North Kazakhstan uranium province, which belongs to the North Tien Shan uranium belt and includes about 50 uranium deposits. As a result, the product of radioactive decay of uranium is radon gas, recognized by the World Health Organization (WHO) as a carcinogen [16].

Other studies, however, reported the opposite effect, with some showing that radiation exposure could lead to global hypermethylation, which was an increase in the overall level of DNA methylation. For example, one study exposed an increase in DNA methylation levels in the sperm of mice exposed to low-dose radiation, which the authors suggest may be a compensatory response to radiation-induced DNA damage [17].

There is evidence to suggest that the change in DNA methylation following ionizing radiation exposure can be dependent on the type of radiation. For example, one study comparing the effects of low-dose gamma radiation and high-energy iron ions found that gamma radiation exposure resulted in global DNA hypomethylation, while iron ion exposure resulted in both hypo- and hypermethylation in a tissue-specific manner [18].

Other studies also reported radiation-induced changes in DNA methylation that are dependent on the dose, timing, and specific tissue or cell type studied [12]. Therefore, the effect of ionizing radiation on DNA methylation may be complex and context-dependent.

It is also worth noting that different types of radiation can induce different types of DNA damage, which may lead to distinct downstream effects on DNA methylation. For example, high-energy charged particles such as iron ions can cause more complex DNA damage than low-energy photons, which could potentially lead to different DNA methylation changes.

Overall, while there is evidence to suggest that the type of ionizing radiation can influence the change in DNA methylation following exposure, further research is needed to fully understand the relationship between radiation type and DNA methylation changes.

Overall, both aging and ionizing radiation exposure can affect DNA methylation patterns, potentially leading to changes in gene expression and increased risk of disease. Understanding the epigenetic effects of these factors is important for developing targeted therapies and improving radiation safety.

It was shown, that several chemical modifications of histones were associated with aging.

Age-related changes in histone methylation were reported in various species, including humans, mice, and fruit flies. For example, decreased levels of H3K4me3 and H3K36me3, two histone marks associated with active transcription, were observed in the brains of aged mice [19].

Histone acetylation, which is generally associated with transcriptional activation, declines with age in various tissues, including the liver, brain, and muscle [20].

Histone phosphorylation was implicated in the regulation of chromatin structure and gene expression, and changed in histone phosphorylation patterns were observed in aged cells and tissues [21].

The level of histone ubiquitination was shown to decrease with age in some tissues, such as the liver and brain [22].

These modifications can alter chromatin structure and gene expression, leading to changes in cellular function and potentially contributing to age-related phenotypes.

The ionizing radiation was shown to affect the chemical modifications of histones. For example, exposure to ionizing radiation was reported to alter histone acetylation and methylation patterns in various cell types, including human lymphoblastoid cells and mouse bone marrow cells [23]. Additionally, ionizing radiation was shown to induce histone phosphorylation and ubiquitination, which are important modifications involved in DNA damage response pathways. The effects of ionizing radiation on histone modifications may contribute to radiation-induced changes in gene expression and cellular function [24].

There is limited research on the coincidence of changes in histone modifications associated with aging and exposure to ionizing radiation. However, some studies suggest that the effects of radiation exposure on histone modifications may accelerate or exacerbate changes associated with aging. For example, it was shown low-dose radiation exposure induced epigenetic changes in mice that resembled changes observed during aging, such as decreased levels of histone H3K4me3 and H3K36me3 marks. These findings suggest that radiation exposure may contribute to premature aging through its effects on histone modifications [25]. However, further research is needed to fully understand the relationship between histone modifications associated with aging and those induced by radiation exposure.

MicroRNAs (miRNAs) are small non-coding RNAs that play important roles in regulating gene expression. There is increasing evidence that miRNAs are involved in the process of aging and age-related diseases, as they regulate key cellular pathways that are associated with aging, such as DNA repair, oxidative stress, and inflammation.

Several studies suggested that exposure to ionizing radiation could alter miRNA expression patterns and contribute to radiation-induced aging. In some studies it was found that low-dose radiation exposure led to changes in miRNA expression in the livers of mice, including upregulation of miRNAs associated with aging and downregulation of miRNAs involved in DNA repair and cell cycle regulation [26]. Similarly, a study by Gao et al. (2017) found that exposure to high-dose radiation led to changes in miRNA expression in the lungs of mice, including upregulation of miRNAs associated with aging and down regulation of miRNAs involved in cell cycle regulation and DNA repair [27].

Radon is a naturally occurring radioactive gas that can accumulate in buildings and can be a source of low-dose ionizing radiation exposure. The exposure to radon led to changes in the expression of several miRNAs in mice, including miR-21 and miR-34a, which are both involved in the DNA damage response and aging-related processes [28]. These findings suggest that exposure to radon may contribute to radiation-induced aging through changes in miRNA expression. Some miRNAs infected during radiation-induced aging are shown in Table.

T a b l e

miRNAs in the radiation-induced aging

miR name	Effect and function	References
miR-34a:	Upregulated in response to ionizing radiation and associated with aging, cellular senescence, and DNA damage response.	[29]
miR-21:	Upregulated in response to ionizing radiation and involved in the regulation of DNA damage response, apoptosis, and cell proliferation. Was also implicated in aging-related processes such as cellular senescence and inflammation.	[30]
miR-29:	Down regulated in response to ionizing radiation and associated with aging-related processes such as tissue fibrosis, inflammation, and extracellular matrix remodeling.	[31]
miR-146a:	Upregulated in response to ionizing radiation and involved in the regulation of inflammation and immune responses. Was also implicated in aging-related processes such as cellular senescence and age-related diseases.	[32]
miR-199a-5p:	miR-199a-5p was significantly upregulated in response to radiation exposure, and that it may be involved in regulating the expression of genes involved in DNA repair and cell cycle regulation	[33]
miR-218-5p:	miR-218-5p was significantly upregulated in response to radiation exposure, and that it may be involved in regulating the expression of genes involved in DNA repair, cell cycle regulation, and apoptosis	[34]
miR-150-5p:	miR-150 was reported to decrease in the circulation of mammals exposed to radiation. miR-150-5p enhanced the radiosensitivity of the cancer cells, possibly by promoting DNA damage and inhibiting DNA repair.	[31]
miR-26b-5p:	miR-26b-5p could be inhibit ATF2 expression to promote DNA damage, apoptosis and radiosensitivity of cancer cells	[35]

Overall, these studies suggest that miRNAs play a role in the process of radiation-induced aging and may be potential targets for interventions to prevent or mitigate radiation-induced damage. However, further research is needed to fully understand the mechanisms underlying these effects and to develop effective strategies for using miRNAs to modulate radiation-induced aging.

MitomiRs are microRNAs that are involved in the regulation of mitochondrial function and metabolism. Mitochondrial dysfunction is a hallmark of aging and is thought to contribute to age-related diseases. Therefore, dysregulation of mitomiRs may play a role in the aging process. Therefore, mitomiRs are thought to play a role in aging-related processes.

Several studies investigated the role of mitomiRs in aging. For example, one study by Burgess et al. (2015) found that the expression of several mitomiRs was altered in the livers of aged mice compared to young mice, including miR-34a, hsa-miR-18a, hsa-miR-431-5p, etc. [36]. These changes were associated with altered mitochondrial function and increased oxidative stress.

Another study found that the expression of several mitomiRs was associated with Alzheimer's Disease, including miR-107 [37], miR-125b [38]. These changes were associated with alterations in mitochondrial function and increased inflammation [39].

Overall, these studies suggest that dysregulation of mitomiRs may play a role in the aging process by contributing to mitochondrial dysfunction and increased oxidative stress and inflammation.

In our last review (2021) we discussed the potential role of mitomiRs in the development of lung cancer induced by exposure to radon, a radioactive gas found in many homes and workplaces [40].

Radon is a naturally occurring radioactive gas that is produced by the decay of uranium in soil, rock, and water. It is colorless, odorless, and tasteless, and can seep into homes and other buildings through cracks in walls, floors, and foundations. Radon exposure is a major cause of lung cancer, and is estimated to be responsible for tens of thousands of deaths from lung cancer each year worldwide.

In this article we highlight several mitomiRs that were shown to be dysregulated in response to radon exposure and might play a role in promoting cancer development, including miR-21, miR-34a, and miR-200c [40].

Based on the above, it can be concluded that mitochondria play an important role in the response of cells to ionizing radiation.

Mitochondria

Radiation-induced aging was shown to be associated with changes in mitochondrial function, including alterations in mitochondrial DNA (mtDNA) and the production of ROS in mitochondria. Mitochondria are organelles responsible for generating cellular energy and play a key role in regulating cellular processes such as apoptosis, metabolism, and signaling. Exposure to ionizing radiation can cause damage to mtDNA and impair mitochondrial function, leading to an increase in ROS production and oxidative stress. This, in turn, can contribute to cellular senescence and aging-related processes.

As mtDNA is located close to the site of ROS production, it is highly susceptible to oxidative damage caused by ionizing radiation. This damage can accumulate over time, leading to mutations and deletions in mtDNA that impair mitochondrial function and contribute to the aging process.

Several studies investigated the relationship between radiation exposure and mtDNA damage. For example, a study by Melin et al. (2022) found that low-dose radiation exposure led to significant increases in mtDNA damage and mutations in the liver tissues of mice [41]. Another study by Liu et al. (2012) reported that radiation exposure caused mtDNA damage and accelerated aging in the brains of mice [42].

One example of mutations in mtDNA leading to aging is mitochondrial myopathy, which is caused by mutations in mtDNA that affect the function of mitochondria, leading to muscle weakness and atrophy. Another example is Leigh syndrome, a rare genetic disorder caused by mutations in mtDNA that affect energy production in the brain, leading to developmental delays, seizures, and other neurological problems. Many studies suggested that radiation exposure can cause mitochondrial dysfunction, exacerbating the symptoms of mitochondrial diseases [43]. The radiation exposure can lead to changes in mitochondrial DNA, which may increase the risk of developing mitochondrial diseases [44].

There is evidence to suggest that radiation exposure can lead to changes in the copy number of free-circulating mitochondrial DNA (cf mtDNA). For example, a study by Borghini et al. (2015) found that exposure to ionizing radiation led to an increase in the levels of free circulating nuclear acids, including the fragment of mtDNA in the blood of cardiologists [45]. Similarly, Bisserier et al. (2021) measured cf-mtDNA levels in blood samples from astronauts before and after long-duration spaceflight on the International Space Station. The researchers found that cf-mtDNA levels increased during spaceflight and remained elevated after return to Earth, suggesting cf-mtDNA abundance might be a biomarker of stress or immune response related to radiation [46].

Our previously results showed a significant difference in the level of cf mtDNA in the blood plasma of healthy volunteers exposed and not exposed to high doses of radon. Moreover, our data indicated that the level of cf mtDNA in the radon-induced lung cancer patients was significantly higher than that of the other study participants with lung cancer [47].

In general, mtDNA copy number tends to decrease with age in many tissues, including blood, muscle, and brain tissue [48]. This decline in mtDNA copy number was suggested to contribute to age-related decline in mitochondrial function and the development of age-related diseases. Yue et al. (2018) used a meta-analysis to examine the relationship between mtDNA copy number and healthy aging in human populations. They found that fewer copies of mtDNA associated with higher risk of cardiovascular disease [49].

It is generally believed that a higher mtDNA copy number is associated with better health and longevity. However, there is no consensus on the exact relationship between mtDNA copy number and aging. Some studies suggested that a higher mtDNA copy number was protective against age-related diseases while others found no association or even a negative association between mtDNA copy number and aging [50]. More research is needed to fully understand the relationship between mtDNA copy number and aging.

Additionally, studies suggested that mitochondria might contribute to the radiation-induced aging process by increasing oxidative stress and inflammation.

Oxidative stress

Oxidative stress is known to play a role in aging. It refers to an imbalance between the production of ROS and the ability of cells to detoxify these reactive molecules. ROS can damage cellular components such as DNA, proteins, and lipids, leading to cellular dysfunction and senescence.

Several studies demonstrated a correlation between oxidative stress and aging. For example, a study by Sastre et al. (2000) found that oxidative damage to mitochondrial DNA increased with age in humans [51]. Another study by Stadtman and Levine suggested that oxidative damage to proteins accumulates with age [52].

In addition, research showed that interventions that reduce oxidative stress can extend lifespan in model organisms such as worms and mice. For instance, a study by Melov et al. found that over expression of antioxidant enzymes in transgenic mice led to increased lifespan [53]. Similarly, a study by Van Raamsdonk and Hekimi found that administration of antioxidants to worms increased their lifespan [54].

Ionizing radiation exposure can lead to the production of ROS, which can damage cells and tissues and contribute to aging. ROS can cause oxidative damage to lipids, proteins, and nucleic acids, including mtDNA. Over time, this damage can accumulate and contribute to age-related decline in cellular and physiological functions.

Several studies investigated the relationship between oxidative stress and radiation-induced aging. It was shown that low-dose ionizing radiation exposure led to increased oxidative stress and accelerated aging in mice. The authors suggested that antioxidant therapies could potentially mitigate the effects of radiation-induced aging [55].

Another study by Hauer-Jensen et al. (2014) investigated the effects of ionizing radiation exposure on the gastrointestinal tract and found that radiation exposure led to increased oxidative stress and inflammation, which contributed to tissue damage and accelerated aging. The authors suggested that antioxidants and anti-inflammatory agents could potentially be used to prevent or treat radiation-induced gastrointestinal damage [56].

Inflammation

Chronic low-grade inflammation, also known as “inflammaging”, is believed to be a contributor to many age-related diseases, including cardiovascular disease, Alzheimer's disease, and cancer. Inflammation can also lead to the accumulation of oxidative stress and damage, which further accelerates the aging process. Several studies demonstrated that levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) increased with age, and that reducing inflammation could improve healthspan and lifespan in animal models.

Exposure to ionizing radiation can cause acute or chronic inflammation, which can contribute to tissue damage and the development of radiation-induced diseases. It is very interesting that all the above mechanisms intersect here.

Ionizing radiation can cause damage to DNA, which triggers a cascade of events leading to the production of pro-inflammatory cytokines and chemokines. These molecules recruit immune cells to the site of radiation exposure and activate the inflammatory response.

Radiation can also cause oxidative stress, which occurs when there is an imbalance between ROS and antioxidants in the body. ROS can damage cellular components and trigger inflammation.

It can activate immune cells such as macrophages and dendritic cells, which release pro-inflammatory cytokines and chemokines. These molecules recruit other immune cells to the site of radiation exposure and amplify the inflammatory response.

The rates of cytokines released by irradiation will vary depending on the assay used to measure them. Thus IL-6, obtained from epithelial cells 24 h after exposure to 1.2 Gy of x-rays, the radiation level increases and determined by ELISA, RNA transcripts increase much earlier (by 1 h), and reach a maximum after 2 h by approximately 8-24 h later [57].

The nuclear factor-kappa B (NF-kB) pathway is a key regulator of inflammation can be activated by radiation, which leading to the production of pro-inflammatory cytokines and chemokines. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that is produced by immune cells and plays a role in regulating the immune response. The level of IL-6 can be influenced by a variety of factors, including radiation exposure.

Studies showed that exposure to ionizing radiation could cause an increase in IL-6 levels in both animals and humans [58]. For example, a study in mice exposed to a single dose of whole-body radiation showed an increase in IL-6 levels in the blood within 24 hours of exposure [59]. Similarly, a study in human subjects exposed to radiation during diagnostic procedures showed an increase in IL-6 levels in the blood.

The magnitude and duration of the increase in IL-6 levels can vary depending on the dose and duration of radiation exposure, as well as individual factors such as age, sex, and genetics. In some cases, the increase in IL-6 levels may be transient and return to baseline levels within a few days, while in other cases it may persist for longer periods.

The increase in IL-6 levels is thought to contribute to the inflammatory response and tissue damage associated with radiation exposure. In addition, IL-6 was implicated in the development of radiation-induced diseases such as radiation pneumonitis and fibrosis. Therefore, monitoring IL-6 levels may be useful in as-

sessing the severity of radiation-induced inflammation and identifying individuals at risk for developing radiation-induced diseases.

Radiation exposure can also inhibit anti-inflammatory pathways. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that is produced by immune cells and plays a role in regulating the immune response. The level of IL-10 can also be influenced by radiation exposure [60].

Studies showed that exposure to ionizing radiation could cause changes in IL-10 levels in both animals and humans. However, the direction and magnitude of these changes can vary depending on the dose and duration of radiation exposure, as well as individual factors such as age, sex, and genetics.

Some studies reported an increase in IL-10 levels after radiation exposure. For example, a study in mice exposed to a single dose of whole-body radiation showed an increase in IL-10 levels in the spleen within 24 hours of exposure [61]. Similarly, a study in human subjects exposed to radiation during cancer treatment showed an increase in IL-10 levels in the blood [62].

Other studies reported a decrease in IL-10 levels after radiation exposure [63]. For example, a study in rats exposed to ionizing radiation showed a decrease in IL-10 levels after radiation exposure [64].

The exact mechanisms underlying the changes in IL-10 levels after radiation exposure are not fully understood. However, it is thought that radiation-induced oxidative stress and inflammation may play a role in modulating IL-10 levels. Further research is needed to better understand the relationship between radiation exposure and IL-10 levels, as well as the implications of these changes for health outcomes.

Aging markers for detection of radiation-induced aging

The accumulation of senescent cells generally contributes to tissue aging in all organ systems and suggests that aging biomarkers can be used to determine the “molecular age” of a patient. Molecular age, in turn, can be used for better risk stratification to maximize treatment efficacy and minimize adverse events [65].

Thus, a significant increase in the frequency of p16-positive melanocytes was found in human skin with age. The data obtained confirm that melanocytes are the main population of senescent cells in the human skin epidermis [66].

Senescent macrophages express high levels of aging-related markers p16. They release pro-inflammatory cytokines that promote chronic inflammation and cause excess ROS production [67].

However, a number of researchers question the usefulness of p16 as a macrophage aging marker, since p16 expression is also upregulated in response to stimuli that induce macrophage polarization to the M2 phenotype. Moreover, activated macrophages in atherosclerotic lesions resemble senescent cells. Therefore, an aging-like phenotype in macrophages may represent a state of physiological activation rather than true aging [68].

The p16 gene belongs to the INK4 gene family and consists of four members: p16 INK4A, p15 INK4B, p18 INK4C, and p19 INK4D, all of which share common biological properties, namely cell growth inhibition and tumor suppression. After p53, p16 is the second most common tumor suppressor gene [69].

p16 (also known as a cyclin-dependent kinase 2A inhibitor) can inhibit the formation of cyclin D-CDK4/6 complexes and thereby prevent retinoblastoma (RB) protein phosphorylation, which in turn contributes to the inhibition of cell cycle gene expression [70].

Cellular senescence may have a twofold effect on carcinogenesis. On the one hand, activation of oncogenes, loss of anti-oncogenes, and DNA damage not only cause apoptosis, but also cause cellular senescence, thereby preventing tumor initiation. Thus, the p16-RB signaling pathway was shown to be involved in oncogene-induced aging and suppression of tumorigenesis [71].

Although aging may prevent cancer by inducing cell cycle arrest, evidence suggests that the chronic inflammation that occurs with aging may contribute to tumorigenesis. In this connection, many studies link high p16 levels with malignant transformation processes and poor outcomes in oncological diseases [72], [73].

It is interesting that the change in p16 level can also be a marker of exposure to radiation. Thus, in irradiated C57BL/6 mice, an increased expression of p16 in macrophages was observed, which indicates the possibility of using p16 as a biomarker of radiation-induced aging [74].

Also biomarker aging is human telomeres, are the exact structure of the DNA-protein complex covering the ends of linear chromosomes. DNA telomeres include numbers of alternating tandem repeats of a double-stranded TTAGGG and an enriched 3' G single-stranded protrusion, called a G-tail. The attachment of the 3'-G-tail to the double-stranded region builds a high-order structure and a three-stranded structure called the T-(telomeric) loop and the D-(shifting) loop. If the DNA polymerase complex stops replicating the 3'-end of the lagging chain in linear chromosomes leads to telomere shortening at each DNA replication cycle during

cell division, leading to a final replication problem. The more the number of cell divisions increases, the TL gradually shortens. If TL decreases to a critical length, cells stop dividing and may fall into cellular senescence or apoptosis [75].

Telomeres nowadays represent one of the powerful biomarkers of aging and pathological conditions associated with aging. Aging is a phenomenon involving multiple pathways and operating at different levels of biological organization of the living system. Different data measuring different parts of the aging process. Estimates of human biological age derived in different ways may differ from one another. Biomarkers of aging can change over the course of a lifetime [76].

Radiation exposure can also cause telomere shortening, as the ionizing radiation can damage DNA and lead to the activation of cellular pathways that accelerate telomere attrition. As a result, telomere length was suggested as a potential biomarker of radiation exposure, as it could provide a means of assessing an individual's risk of radiation-induced health effects.

Studies showed that individuals exposed to ionizing radiation, such as nuclear plant workers [77] or cancer patients undergoing radiotherapy [78] had shorter telomeres compared to unexposed individuals. However, other factors such as age, lifestyle, and environmental exposures can also influence telomere length, making it difficult to use telomere length as a definitive marker of radiation exposure.

In conclusion, while telomere length can be affected by radiation exposure, it is not a reliable marker on its own and should be considered alongside other indicators of exposure to ionizing radiation, such as dosimetry measurements or biomarkers of DNA damage.

Cytokines can also be classified as biomarkers of radiation-induced aging. Pro-inflammatory cytokines are a class of signaling molecules that are involved in the immune response and play an important role in regulating inflammation. Research was suggested that chronic inflammation might be a contributing factor to the aging process and the development of age-related diseases.

Exposure to ionizing radiation was shown to induce chronic inflammation, which may contribute to radiation-induced aging. Studies demonstrated that radiation exposure could lead to increased levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) [79].

For example, a study of [80] examined the levels of various cytokines in the blood of mice exposed to ionizing radiation. The researchers found that radiation exposure led to an increase in the levels of pro-inflammatory cytokines, including IL-6 and TNF-α, and that these increases persisted for several weeks after the exposure.

Another study found that radiation exposure led to an increase in the levels of IL-6 and IL-1β, and that these increases were associated with lung and liver radiation-induced damage [81].

Overall, these studies suggest that pro-inflammatory cytokines may serve as a marker of radiation-induced aging and could potentially be used to assess an individual's risk of developing age-related diseases following exposure to ionizing radiation. However, further research is needed to fully understand the relationship between radiation-induced inflammation and aging, and to identify the most reliable and sensitive biomarkers of this process.

Conclusions

Due to the presence of the densely populated territories in the Republic of Kazakhstan contaminated with radionuclides as a result of nuclear weapons testing at the Semipalatinsk test site, mining and processing of uranium ores, high levels of radon radioactive gas, there is a significant threat to the health of our population [82].

A number of studies showed that ionizing radiation induced the development of cellular senescence, and as a result, increased the risk of developing age-associated diseases such as cancer, neurodegenerative diseases and diseases of the cardiovascular system. Therefore the issue of developing preventive measures that could reduce the adverse effects of ionizing radiation on the Kazakhstan population is acute. But such developments require a complete understanding of the mechanism of radiation-induced senescence. And although the mechanisms of radiation-induced senescence are gradually being studied, a lot of things still remain unclear.

Thus, miRNAs was shown to play an important role in the radiation response of cells. miRNAs are short non-coding RNAs involved in the regulation of almost all cellular processes, including the functioning of such important organelles as mitochondria.

Mitochondria are unique organelles that, on the one hand, have their own genome, the functioning of which is subordinate to the nuclear genome, and on the other hand, mitochondria are able to regulate the

functioning of the nuclear genome. There is no doubt that mitochondria play a key role in cellular responses to various types of ionizing radiation. Thus, it was shown that ionizing radiation leads to an increase in mitochondrial DNA, levels of intracellular reactive oxygen species (ROS) in the absence of increased mitochondrial activity, a change in the transmembrane potential, and, ultimately, the development of mitochondrial dysfunction in irradiated cells.

MitomiRs are microRNAs that regulate the expression of mitochondrial genes. However, there is no information in the literature about changes in the expression profile of mitomiRs under different types of ionizing radiation, or about the role of these regulatory molecules in radiation-induced senescence. At the same time, the study of the relationship between mitochondria, mitomiR and radiation in the senescence process will expand the range of possible approaches to slowing down the rate of senescence, delaying or completely stopping the development of age-associated diseases, especially for people living under conditions of exposure to high doses of ionizing radiation.

Radiation-induced aging can have significant implications for the preservation of human health, both in terms of preventing age-related diseases and improving outcomes for individuals who have been exposed to radiation.

Understanding the mechanisms of radiation-induced aging can help identify potential interventions to mitigate the effects of radiation exposure. For example, researchers may be able to identify drugs or other therapies that can help protect cells from radiation-induced damage, or promote the repair of damaged cells.

Radiation-induced aging can serve as a model for studying natural aging. Many of the molecular and cellular changes that occur during radiation-induced aging are similar to those that occur during natural aging, such as telomere shortening, oxidative stress, and inflammation. By studying radiation-induced aging, researchers can gain insight into the mechanisms of natural aging, and identify potential targets for interventions to improve healthspan and lifespan.

Radiation exposure is a significant risk factor for a range of age-related diseases, including cardiovascular disease, neurodegenerative disorders, and cancer. By studying the effects of radiation on aging at the cellular and molecular level, researchers can gain insight into the underlying mechanisms of these diseases, and identify potential targets for prevention and treatment.

Overall, understanding the mechanisms of radiation-induced aging can have important implications for the preservation of human health. By identifying potential interventions to mitigate the effects of radiation exposure and studying the mechanisms of age-related diseases, researchers can work towards improving health outcomes for individuals who have been exposed to radiation and preventing age-related diseases more broadly.

Acknowledgements

This research was supported by a grant from the Ministry of Science and Higher Education of the Republic of Kazakhstan under award number AP14870508.

References

1 Schumacher, B., Pothof, J., Vijg, J., & Hoeijmakers, J.H.J. (2021). The central role of DNA damage in the ageing process. *Nature*, *592*(7856):695-703. doi: 10.1038/s41586-021-03307-7.

2 Schmeer, C., Kretz, A., Wengerodt, D., Stojiljkovic, M., & Witte, O.W. (2019). Dissecting Aging and Senescence-Current Concepts and Open Lessons. *Cells, 8*(11):1446. doi: 10.3390/cells8111446.

3 Miwa, S., Kashyap, S., Chini, E., & von Zglinicki, T. (2022). Mitochondrial dysfunction in cell senescence and aging. *J Clin Invest, 132*(13), e158447. doi: 10.1172/JCI158447.

4 Todorova, P.K., Fletcher-Sananikone, E., Mukherjee, B., Kollipara, R., Vemireddy, V., Xie, X.J., Guida, P.M., Story, M.D., Hatanpaa, K., Habib, A.A., Kittler, R., Bachoo, R., Hromas, R., Floyd, J.R., & Burma, S. (2019). Radiation-Induced DNA Damage Cooperates with Heterozygosity of TP53 and PTEN to Generate High-Grade Gliomas. *Cancer Res, 79*(14):3749-3761. doi: 10.1158/0008-5472.CAN-19-0680.

5 Blackford, A.N., & Jackson, S.P. (2017). ATM, ATR, and DNA-PK: The Trinity at the Heart of the DNA Damage Response. *Mol Cell*, *66*(6):801-817. doi: 10.1016/j.molcel.2017.05.015.

6 Lu, H., Davis, A.J., & Human Rec, Q. (2021). Helicases in DNA Double-Strand Break Repair. Front *Cell Dev Biol*, 9:640755. doi: 10.3389/fcell.2021.640755.

7 Inagawa, T., Wennink, T., Lebbink, J.H.G., Keijzers, G., Florea, B.I., Verkaik, N.S., & van Gent, D.C. (2020). C-Terminal Extensions of Ku70 and Ku80 Differentially Influence DNA End Binding Properties. *Int J Mol Sci, 21*(18):6725. doi: 10.3390/ijms21186725.

8 White, R.R., & Vijg, J. (2016). Do DNA Double-Strand Breaks Drive Aging? *Mol Cell*, *63*(5):729-38. doi: 10.1016/j.molcel.2016.08.004.

9 Blimkie, M.S., Fung, L.C., Petoukhov, E.S., Girard, C., & Klokov, D. (2014). Repair of DNA double-strand breaks is not modulated by low-dose gamma radiation in C57BL/6J mice. *Radiat Res*, *181*(5):548-59. doi: 10.1667/RR13324.1.

10 Kumar, N., Theil, A.F., Roginskaya, V., Ali, Y., Calderon, M., Watkins, S.C., Barnes, R.P., Opresko, P.L., Pines, A., Lans, H., Vermeulen, W., & Van Houten, B. (2022). Global and transcription-coupled repair of 8-oxoG is initiated by nucleotide excision repair proteins. *Nat Commun., 13*(1):974. doi: 10.1038/s41467-022-28642-9.

11 Fouquerel, E., Barnes, R.P., Uttam, S., Watkins, S.C., Bruchez, M.P., & Opresko, P.L. (2019). Targeted and Persistent 8-Oxoguanine Base Damage at Telomeres Promotes Telomere Loss and Crisis. *Mol Cell*, *75*(1):117-130.e6. doi: 10.1016/j.molcel.2019.04.024.

12 Belli, M., & Tabocchini, M.A. (2020). Ionizing Radiation-Induced Epigenetic Modifications and Their Relevance to Radiation Protection. *Int J Mol Sci*, *21*(17):5993. doi: 10.3390/ijms21175993.

13 Koturbash, I., Miousse, I.R., Sridharan, V., Nzabarushimana, E., Skinner, C.M., Melnyk, S.B., Pavliv, O., Hauer-Jensen, M., Nelson, G.A., & Boerma, M. (2016). Radiation-induced changes in DNA methylation of repetitive elements in the mouse heart. *Mutat Res*, *787*:43-53. doi: 10.1016/j.mrfmmm.2016.02.009.

14 Su, S., Jin, Y., Zhang, W., Yang, L., Shen, Y., Cao, Y., & Tong, J. (2006). Aberrant promoter methylation of p16(INK4a) and O(6)-methylguanine-DNA methyltransferase genes in workers at a Chinese uranium mine. *J Occup Health*, *48*(4):261-6. doi: 10.1539/joh.48.261.

15 Bersimbaev, R.I., Lindholm, C., Tankimanova, M.K., Djansugarova, L.B., Mamyrbaeva, Z.Zh., Mustonen, R., Dubrova Y.E., Hulten, M., Suomela, M., Auvinen, A., & Salomaa, S. (2002). Three generation study of population living the vicinity of the Semipalatinsk nuclear test site — biosample database and population characteristics. *Helsinki: STUK-Radiation and Nuclear Safety Authority.*

16 WHO. (2021). *Radon*. World Health Organization. [Electronic resource]. — Access mode: https://www.who.int/ru/news-room/fact-sheets/detail/radon-and-health.

17 Mughal, S.K., Myazin, A.E., Zhavoronkov, L.P., Rubanovich, A.V., & Dubrova, Y.E. (2012). The dose and dose-rate effects of paternal irradiation on transgenerational instability in mice: a radiotherapy connection. *PLoS One*, *7*(7): e41300. doi: 10.1371/journal.pone.0041300.

18 Legendre, A., Elmhiri, G., Gloaguen, C., Magneron, V., Kereselidze, D., Saci, N., Elie, C., Vaysset, É., Benadjaoud, M.M., Tack, K., Grison, S., & Souidi, M. (2019). Multigenerational exposure to uranium changes morphometric parameters and global DNA methylation in rat sperm. *C R Biol*, *342*(5-6):175-185. doi: 10.1016/j.crvi.2019.07.002.

19 Sun, Z., Zhang, Y., Jia, J., Fang, Y., Tang, Y., Wu, H., & Fang, D. (2020). H3K36me3, message from chromatin to DNA damage repair. *Cell Biosci*, 10:9. doi: 10.1186/s13578-020-0374-z.

20 Kumar, A., Choi, K.H., Renthal, W., Tsankova, N.M., Theobald, D.E., Truong, H.T., Russo, S.J., Laplant, Q., Sasaki, T.S., Whistler, K.N., Neve, R.L, Self, D.W., & Nestler, E.J. (2005). Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron, *48*(2):303-14. doi: 20.1016/j.neuron.2005.09.023.

21 O'Sullivan, R.J., & Karlseder, J. (2012). The great unravelling: chromatin as a modulator of the aging process. *Trends Biochem Sci*, *37*(11):466-76. doi: 10.1016/j.tibs.2012.08.001.

22 Uckelmann, M., & Sixma, T.K. (2017). Histone ubiquitination in the DNA damage response. *DNA Repair (Amst), 56*:92-101. doi: 10.1016/j.dnarep.2017.06.011.

23 Peng, Q., Weng, K., Li, S., Xu, R., Wang, Y., & Wu, Y.A. (2021). Perspective of Epigenetic Regulation in Radiotherapy. *Front Cell Dev Biol, 9*:624312. doi: 10.3389/fcell.2021.624312.

24 Di Nisio, E., Lupo, G., Licursi, V., & Negri, R. (2021). The Role of Histone Lysine Methylation in the Response of Mammalian Cells to Ionizing Radiation. *Front Genet*, 12:639602. doi: 10.3389/fgene.2021.639602.

25 Friedl, A.A., Mazurek, B., & Seiler, D.M. (2012). Radiation-induced alterations in histone modification patterns and their potential impact on short-term radiation effects. *Front Oncol*, 2:117. doi: 10.3389/fonc.2012.00117.

26 Liang, X., Zheng, S., Cui, J., Yu, D., Yang, G., Zhou, L., Wang, B., Cai, L., & Li, W. (2018). Alterations of MicroRNA Expression in the Liver, Heart, and Testis of Mice Upon Exposure to Repeated Low-Dose Radiation. *Dose Response*, *16*(3):1559325818799561. doi: 10.1177/1559325818799561.

27 Gao, F., Liu, P., Narayanan, J., Yang, M., Fish, B.L., Liu, Y., Liang, M., Jacobs, E.R., & Medhora, M. (2017). Changes in miRNA in the lung and whole blood after whole thorax irradiation in rats. *Sci Rep*, 7:44132. doi: 10.1038/srep44132.

28 Pei, W., Tao, L., Zhang, L.W, Zhang, S., Cao, J., Jiao, Y., Tong, J., & Nie, J. (2017). Circular RNA profiles in mouse lung tissue induced by radon. *Environ Health Prev Med*, *22*(1):36. doi: 10.1186/s12199-017-0627-6.

29 Suh, N. (2018). MicroRNA controls of cellular senescence. *BMB Rep*, *51*(10):493-499. doi: 10.5483/BMBRep.2018.51.10.209.

30 Liu, C., Li, B., Cheng, Y., Lin, J., Hao, J., Zhang, S., Mitchel, R.E., Sun, D., Ni, J., Zhao, L., Gao, F., & Cai, J. (2011). MiR-1 plays an important role in radiation induced carcinogenesis in BALB/c mice by directly targeting the tumor suppressor gene Bigh3. *Int J Biol Sci*, *7*(3):347-63. doi: 10.7150/ijbs.7.347.

31 Dinh, T.-K.T., Fendler, W., Chałubińska-Fendler, J., Acharya, S.S., O'Leary, C., & Deraska, P.V., et al. (2016). Circulating miR-29a and miR-150 Correlate with Delivered Dose during Thoracic Radiation Therapy for Non-small Cell Lung Cancer. *Radiat. Oncol.* 11, 61. 10.1186/s13014-016-0636-4.

32 Jia, M., & Wang, Z. (2022). MicroRNAs as Biomarkers for Ionizing Radiation Injury. Front *Cell Dev Biol*, 10:861451. doi: 10.3389/fcell.2022.861451.

33 Baek, D.W., Kim, G., Kang, B.W., Kim, H.J., Park, S.Y., Park, J.S., et al. (2020). High Expression of microRNA-199a-5p Is Associated with superior Clinical Outcomes in Patients with Locally Advanced Rectal Cancer. *J. Cancer Res. Clin. Oncol, 146*(1), 105–115. 10.1007/s00432-019-03099-4

34 Chen, X., Xu, Y., Jiang, L., & Tan, Q. (2021). miRNA -218-5p Increases Cell Sensitivity by Inhibiting PRKDC Activity in Radiation-Resistant Lung Carcinoma Cells. *Thorac. Cancer, 12*(10), 1549–1557. 10.1111/1759-7714.13939

35 Han, F., Huang, D., Huang, X., Wang, W., Yang, S., & Chen, S. (2020). Exosomal microRNA-26b-5p Down-Regulates ATF2 to Enhance Radiosensitivity of Lung Adenocarcinoma Cells. *J. Cel Mol Med, 24*(14), 7730–7742. 10.1111/jcmm.15402

36 Burgess, K.S., Philips, S., Benson, E.A., Desta, Z., Gaedigk, A., Gaedigk, R., Segar, M.W., Liu, Y., & Skaar, T.C. (2015). Age-Related Changes in MicroRNA Expression and Pharmacogenes in Human Liver. *Clin Pharmacol Ther*, *98*(2):205-15. doi: 10.1002/cpt.145.

37 Shu, B., Zhang, X., Du, G., Fu, Q., & Huang, L. (2018). MicroRNA-107 prevents amyloid-β-induced neurotoxicity and memory impairment in mice. Int. *J. Mol. Med*, 41:1665–1672. doi: 10.3892/ijmm.2017.3339.

38 Ma, X., Liu, L., & Meng, J. (2017). MicroRNA-125b promotes neurons cell apoptosis and Tau phosphorylation in Alzheimer's disease. *Neurosci. Lett*, *661*:57–62. doi: 10.1016/j.neulet.2017.09.043.

39 John, A., Kubosumi, A., & Reddy, P.H. (2020). Mitochondrial MicroRNAs in Aging and Neurodegenerative Diseases. *Cells*, *9*(6):1345. doi: 10.3390/cells9061345.

40 Kussainova, A., Bulgakova, O., Aripova, A., Khalid, Z., Bersimbaev, R., & Izzotti, A. (2022). The Role of Mitochondrial miRNAs in the Development of Radon-Induced Lung Cancer. *Biomedicines*, *10*(2):428. doi: 10.3390/biomedicines10020428.

41 Melin, N., Yarahmadov, T., Sanchez-Taltavull, D., Birrer, F.E., Brodie, T.M., Petit, B., Felser, A., Nuoffer, J.M., Montani, M., Vozenin, M.C., Herrmann, E., Candinas, D., Aebersold, D.M., & Stroka, D. (2022). A new mouse model of radiation-induced liver disease reveals mitochondrial dysfunction as an underlying fibrotic stimulus. *JHEP Rep*, *4*(7):100508. doi: 10.1016/j.jhepr.2022.100508.

42 Liu, G.S., Zhang, Z.S., Yang, B., & He, W. (2012). Resveratrol attenuates oxidative damage and ameliorates cognitive impairment in the brain of senescence-accelerated mice. *Life Sci*, *91*(17-18):872-7. doi: 10.1016/j.lfs.2012.08.033.

43 Knottnerus, S.J.G., Bleeker, J.C., Wüst, R.C.I., Ferdinandusse, S., IJlst, L., Wijburg, F.A., Wanders, R.J.A., Visser, G., & Houtkooper, R.H. (2018). Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. *Rev Endocr Metab Disord*, *19*(1):93-106. doi: 10.1007/s11154-018-9448-1.

44 Livingston, K., Schlaak, R.A., Puckett, L.L., & Bergom, C. (2020). The Role of Mitochondrial Dysfunction in Radiation-Induced Heart Disease: From Bench to Bedside. *Front Cardiovasc Med*, 7:20. doi: 10.3389/fcvm.2020.00020.

45 Borghini, A., Mercuri, A., Turchi, S., Chiesa, M.R., Piccaluga, E., & Andreassi, M.G. (2015). Increased circulating cell-free DNA levels and mtDNA fragments in interventional cardiologists occupationally exposed to low levels of ionizing radiation. *Environ Mol Mutagen*, *56*(3):293-300. doi: 10.1002/em.21917.

46 Bisserier, M., Shanmughapriya, S., Rai, A.K., Gonzalez, C., Brojakowska, A., Garikipati, V.N.S., Madesh, M., Mills, P.J., Walsh, K., Arakelyan, A., Kishore, R., Hadri, L., & Goukassian, D.A. (2021). Cell-Free Mitochondrial DNA as a Potential Biomarker for Astronauts' Health. *J Am Heart Assoc*, (21): e022055. doi: 10.1161/JAHA.121.022055.

47 Bulgakova, O., Kussainova, A., Kakabayev, A., Aripova, A., Baikenova, G., Izzotti, A., & Bersimbaev, R. (2022). The level of free-circulating mtDNA in patients with radon-induced lung cancer. *Environ Res*, 1; 207, 112215. doi: 10.1016/j.envres.2021.112215.

48 Mengel-From, J., Thinggaard, M., Dalgård, C., Kyvik, K.O., Christensen, K., & Christiansen, L. (2014). Mitochondrial DNA copy number in peripheral blood cells declines with age and is associated with general health among elderly. *Hum Genet*, *133*(9):1149-59. doi: 10.1007/s00439-014-1458-9.

49 Yue, P., Jing, S., Liu, L., Ma, F., Zhang, Y., Wang, C., Duan, H., Zhou, K., Hua, Y., Wu, G., & Li, Y. (2018). Association between mitochondrial DNA copy number and cardiovascular disease: Current evidence based on a systematic review and meta-analysis. *PLoS One*, *13*(11): e0206003. doi: 10.1371/journal.pone.0206003.

50 Pinti, M., Cevenini, E., Nasi, M., De Biasi, S., Salvioli, S., Monti, D., Benatti, S., Gibellini, L., Cotichini, R., Stazi, M.A., Trenti, T., Franceschi, C., & Cossarizza, A. (2014). Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging". *Eur J Immunol*, *44*(5):1552-62. doi: 10.1002/eji.201343921.

51 Sastre, J., Pallardó, F.V., & Viña, J. (2000). Mitochondrial oxidative stress plays a key role in aging and apoptosis. *IUBMB Life*, *49*(5):427-35. doi: 10.1080/152165400410281.

52 Stadtman, E.R., & Levine, R.L. (2003). Free radical-mediated oxidation of free amino acids and amino acid residues in proteins. *Amino Acids*, *25*(3-4):207-18. doi: 10.1007/s00726-003-0011-2.

53 Melov, S., Coskun, P., Patel, M., Tuinstra, R., Cottrell, B., Jun, A.S., Zastawny, T.H., Dizdaroglu, M., Goodman, S.I., Huang, T.T., Miziorko, H., Epstein, C.J., & Wallace, D.C. (1999). Mitochondrial disease in superoxide dismutase 2 mutant mice. *Proc Natl Acad Sci USA*, *96*(3):846-51. doi: 10.1073/pnas.96.3.846.

54 Van Raamsdonk, J.M., & Hekimi, S. (2012). Superoxide dismutase is dispensable for normal animal lifespan. *Proc Natl Acad Sci U S A*, *109*(15):5785-90. doi: 10.1073/pnas.1116158109.

55 Tharmalingam, S., Sreetharan, S., Kulesza, A.V., Boreham, D.R., & Tai, T.C. (2017). Low-Dose Ionizing Radiation Exposure, Oxidative Stress and Epigenetic Programing of Health and Disease. *Radiat Res*, *188*(4.2):525-538. doi: 10.1667/RR14587.1.

56 Hauer-Jensen, M., Denham, J.W., & Andreyev, H.J. (2014). Radiation enteropathy — pathogenesis, treatment and prevention. Nat Rev Gastroenterol Hepatol, *11*(8):470-9. doi: 10.1038/nrgastro.2014.46.

57 Sridharan, D.M., Asaithamby, A., Blattnig, S.R., Costes, S.V., Doetsch, P.W., Dynan, W.S., Hahnfeldt, P., Hlatky, L., Kidane, Y., Kronenberg, A., Naidu, M.D., Peterson, L.E., Plante, I., Ponomarev, A.L., Saha, J., Snijders, A.M., Srinivasan, K., Tang, J., Werner, E., & Pluth, J.M. (2016). Evaluating biomarkers to model cancer risk post cosmic ray exposure. *Life Sci Space Res (Amst),* 9:19-47. doi: 10.1016/j.lssr.2016.05.004.

58 Lumniczky, K., Impens, N., Armengol, G., Candéias, S., Georgakilas, A.G., Hornhardt, S., Martin, O.A., Rödel, F., & Schaue, D. (2021). Low dose ionizing radiation effects on the immune system. *Environ Int*, *149*:106212. doi: 10.1016/j.envint.2020.106212.

59 Lierova, A., Jelicova, M., Nemcova, M., Proksova, M., Pejchal, J., Zarybnicka, L., & Sinkorova, Z. (2018). Cytokines and radiation-induced pulmonary injuries. *J Radiat Res*, *59*(6):709-753. doi: 10.1093/jrr/rry067.

60 Zhang, Q., Chen, X., Luo, Y., Ren, H., & Qiao, T. Fuzi. (2017). Enhances Anti-Tumor Efficacy of Radiotherapy on Lung Cancer. *J Cancer*, 8(19):3945-3951. doi: 10.7150/jca.22162.

61 Liu, X., Liu, Z., Wang, D., Han, Y., Hu, S., Xie, Y., Liu, Y., Zhu, M., Guan, H., Gu, Y., & Zhou, P.K. (2020). Effects of low dose radiation on immune cells subsets and cytokines in mice. *Toxicol Res (Camb)*, 9(3):249-262. doi: 10.1093/toxres/tfaa017.

62 Aneva, N., Zaharieva, E., Katsarska, O., Savova, G., Stankova, K., Djounova, J., & Boteva, R. (2019). Inflammatory profile dysregulation in nuclear workers occupationally exposed to low-dose gamma radiation. *J Radiat Res*, *60*(6):768-779. doi: 10.1093/jrr/rrz059.

63 Haase, M.G., Klawitter, A., Geyer, P., & Baretton, G.B. (2007). Expression of the immunomodulator IL-10 in type I pneumocytes of the rat: alterations of IL-10 expression in radiation-induced lung damage. *J Histochem Cytochem*, *55*(11), 1167-72. doi: 10.1369/jhc.7A7173.2007.

64 Hussien, S.M., & Rashed, E.R. (2023). Immune system modulation by low-dose ionizing radiation-induced adaptive response. *Int J Immunopathol Pharmacol*, *37*, 3946320231172080. doi: 10.1177/03946320231172080.

65 Muss, H.B., Smitherman, A., Wood, W.A., Nyrop, K., Tuchman, S., Randhawa, P.K., Entwistle, A.R., Mitin, N., & Shachar, S.S. (2020). p16 a biomarker of aging and tolerance for cancer therapy. *Transl Cancer Res*, *9*(9), 5732-5742. doi: 10.21037/tcr.2020.03.39.

66 Victorelli, S., Lagnado, A., Halim, J., Moore, W., Talbot, D., Barrett, K., Chapman, J., Birch, J., Ogrodnik, M., Meves, A., Pawlikowski, J.S., Jurk, D., Adams, P.D., van Heemst, D., Beekman, M., Slagboom, P.E., Gunn, D.A., & Passos, J.F. (2019). Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction. *EMBO J*, *38*(23): e101982. doi: 10.15252/embj.2019101982.

67 Sadhu, S., Decker, C., Sansbury, B.E., Marinello, M., Seyfried, A., Howard, J., Mori, M., Hosseini, Z., Arunachalam, T., Finn, A.V., Lamar, J.M., Jourd'heuil, D., Guo, L., MacNamara, K.C, Spite, M., & Fredman, G. (2021). Radiation-Induced Macrophage Senescence Impairs Resolution Programs and Drives Cardiovascular Inflammation. *J Immunol, 207*(7):1812-1823. doi: 10.4049/jimmunol.2100284.

68 Hall, B.M., Balan, V., Gleiberman, A.S., Strom, E., Krasnov, P., Virtuoso, L.P., Rydkina, E., Vujcic, S., Balan, K., Gitlin, I.I., Leonova, K.I., Consiglio, C.R., Gollnick, S.O., Chernova, O.B., & Gudkov, A.V. (2017). p16(Ink4a) and senescence-associated β-galactosidase can be induced in macrophages as part of a reversible response to physiological stimuli. *Aging (Albany NY), 9*(8):1867-1884. doi: 10.18632/aging.101268.

69 Sand, F.L., Nielsen, D.M.B., Frederiksen, M.H., Rasmussen, C.L., & Kjaer, S.K. (2019). The prognostic value of p16 and p53 expression for survival after vulvar cancer: A systematic review and meta-analysis. *Gynecol Oncol*, *152*(1):208-217. doi: 10.1016/j.ygyno.2018.10.015.

70 Huang, W., Hickson, L.J., Eirin, A., Kirkland, J.L., & Lerman, L.O. (2022). Cellular senescence: the good, the bad and the unknown. *Nat Rev Nephrol*, *18*(10):611-627. doi: 10.1038/s41581-022-00601-z. Epub 2022 Aug 3.

71 Yasaei, H., Gilham, E., Pickles, J.C., Roberts, T.P., O'Donovan, M., & Newbold, R.F. (2013). Carcinogen-specific mutational and epigenetic alterations in INK4A, INK4B and p53 tumour-suppressor genes drive induced senescence bypass in normal diploid mammalian cells. *Oncogene*, *32*(2):171-9. doi: 10.1038/onc.2012.45.

72 Yasuda, T., Koiwa, M., Yonemura, A., Miyake, K., Kariya, R., Kubota, S., Yokomizo-Nakano, T., Yasuda-Yoshihara, N., Uchihara, T., Itoyama, R., Bu, L., Fu, L., Arima, K., Izumi, D., Iwagami, S., Eto, K., Iwatsuki, M., Baba, Y., Yoshida, N., Ohguchi, H., Okada, S., Matsusaki, K., Sashida, G., Takahashi, A., Tan, P., Baba, H., & Ishimoto, T. (2021). Inflammation-driven senescence-associated secretory phenotype in cancer-associated fibroblasts enhances peritoneal dissemination. *Cell Rep, 34*(8):108779. doi: 10.1016/j.celrep.2021.108779.

73 Raju, K., Raghuveer, C.V., Sheela, S.R., Natarajan, A., Jagadish, T.V., Sunil, B.N., & Sharat, B. (2022). Evaluation of enzyme-linked immunosorbent assay plasma p16INK4a protein in squamous cell carcinoma in uterine cervix: A case-control study. *J Cancer Res Ther*, *18*(1):152-157. doi: 10.4103/jcrt.JCRT_1290_20.

74 Sadhu, S., Decker, C., Sansbury, B.E., Marinello, M., Seyfried, A., Howard, J., Mori, M., Hosseini, Z., Arunachalam, T., Finn, A.V., Lamar, J.M., Jourd'heuil, D., Guo, L., MacNamara, K.C., Spite, M., & Fredman, G. (2021). Radiation-Induced Macrophage Senescence Impairs Resolution Programs and Drives Cardiovascular Inflammation. *J Immunol, 207*(7):1812-1823. doi: 10.4049/jimmunol.2100284.

75 Tian, Y., Wang, S., Jiao, F., Kong, Q., Liu, C., & Wu, Y. (2019). Telomere Length: A Potential Biomarker for the Risk and Prognosis of Stroke. *Front Neurol*, 10:624. doi: 10.3389/fneur.2019.00624. PMID: 31263449; PMCID: PMC6585102.

76 Vaiserman, A., & Krasnienkov, D. (2021). Telomere Length as a Marker of Biological Age: State-of-the-Art, Open Issues, and Future Perspectives. *Front Genet*, 11:630186. doi: 10.3389/fgene.2020.630186.

77 Lustig, A., Shterev, I., Geyer, S., Shi, A., Hu, Y., Morishita, Y., Nagamura, H., Sasaki, K., Maki, M., Hayashi, I., Furukawa, K., Yoshida, K., Kajimura, J., Kyoizumi, S., Kusunoki, Y., Ohishi, W., Nakachi, K., Weng, N.P., & Hayashi, T. (2016). Long term effects of radiation exposure on telomere lengths of leukocytes and its associated biomarkers among atomic-bomb survivors. *Oncotarge*t, *7*(26):38988-38998. doi: 10.18632/oncotarget.8801.

78 Pauleck, S., Sinnott, J.A., Zheng, Y.L., Gadalla, S.M., Viskochil, R., Haaland, B., Cawthon, R.M., Hoffmeister, A., & Hardikar, S. (2023). Association of Telomere Length with Colorectal Cancer Risk and Prognosis: A Systematic Review and Meta-Analysis. *Cancers (Basel), 15*(4):1159. doi: 10.3390/cancers15041159.

79 Liu, X., Shao, C., & Fu, J. (2021). Promising Biomarkers of Radiation-Induced Lung Injury: A Review. *Biomedicines*, *9*(9):1181. doi: 10.3390/biomedicines9091181.

80 Zhang, et al. Zhang, M., Yin, L., & Zhang, K. et al. (2012). Response patterns of cytokines/chemokines in two murine strains after irradiation. *Cytokine*, *58*:169–77.

81 Sultan, S., Ahmad, S., & Rave-Fränk, M. et al. (2016). Induction of lipocalin2 in a rat model of lung irradiation. *Int J Mol Sci*, *17*.

82 Bersimbaev, R.I., & Bulgakova, O. (2015). The health effects of radon and uranium on the population of Kazakhstan. *Genes Environ*, *37*:18. doi: 10.1186/s41021-015-0019-3.

О.В. Булгакова, Н.Б. Режепова

Радиация әсерінен қартаюдың молекулалық механизмдері

Радиацияның әсерінен қартаю — көптеген молекулалық механизмдерді қамтитын күрделі процесс. Радиацияның әсерінен қартаюдың негізгі механизмдерінің бірі — тотығу күйзелісі. Сәулеленудің әсері реактивті оттегі түрлерінің (ROS) түзілуіне әкеліп соғады, бұл ДНҚ-ға, ақуыздарға және басқа жасушалық компоненттерге зақым келтіруі мүмкін. Осы механизмдерден басқа, радиацияның әсерінен қартаю ген экспрессиясының, жасушалық метаболизмнің және эпигенетикалық модификациядағы өзгерістерді қамтуы мүмкін. Бұл өзгерістер әртүрлі жасушалық жолдардың жұмысына әсер етуі және қартаю процесіне ықпал етуі мүмкін. Радиация әсерінен болатын қартаюдың молекулалық механизмдерін түсіну оның әсерін азайту стратегияларын әзірлеу үшін өте маңызды. Ықтимал араласуларға тотығу күйзелісімен күресу, ДНҚ-ны қалпына келтіруге көмектесу, эпигенетикалық ландшафтты өзгерту және жасушалық метаболизмді модуляциялау кіреді. Дегенмен, радиациядан туындаған қартаюға қатысатын күрделі молекулалық жолдарды толығымен түсіндіру және тиімді терапиялық тәсілдерді анықтау үшін қосымша зерттеулер қажет. Тұтастай алғанда, осы шолуда қарастырылған радиацияның қартаюға әсер етуінің молекулалық механизмдері радиациядан туындаған қартаюға жаңа көзқараспен қарауға және араласудың жаңа мақсаттарын анықтауға мүмкіндік береді.

Кілт сөздер: қартаю, ДНҚ зақымдануы, теломерлер, митохондрия, микроРНҚ, қабыну, p16, радиацияның әсерінен қартаю.

О.В. Булгакова, Н.Б. Режепова

Молекулярные механизмы радиационно-индуцированного старения

Радиационно-индуцированное старение — это сложный процесс, который включает в себя множество молекулярных механизмов. Одним из основных механизмов, лежащих в основе радиационно-индуцированного старения, является окислительный стресс. Воздействие радиации может привести к образованию реактивных форм кислорода (ROS), которые могут вызвать повреждение ДНК, белков и других клеточных компонентов. Помимо этих механизмов, радиационно-индуцированное старение также может включать изменения в экспрессии генов, клеточном метаболизме и эпигенетических модификациях. Эти изменения могут влиять на функционирование различных клеточных путей и способствовать процессу старения. Понимание молекулярных механизмов радиационно-индуцированного старения имеет решающее значение для разработки стратегий по смягчению его последствий. Потенциальные меры вмешательства включают борьбу с окислительным стрессом, содействие восстановлению ДНК, изменение эпигенетического ландшафта и модуляцию клеточного метаболизма. Однако для полного выяснения сложных молекулярных путей, участвующих в радиационно-индуцированном старении, и определения эффективных терапевтических подходов необходимы дальнейшие исследования. В целом, молекулярные механизмы влияния радиации на старение, рассмотренные в данном обзоре, позволяют по-новому взглянуть на радиационно-индуцированное старение и определить новые мишени для вмешательства.

Ключевые слова: старение, повреждение ДНК, теломеры, митохондрия, микроРНК, воспаление, p16, радиационно-индуцированное старение.